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26. A method of producing a non-cell binding antibody for inducing immunological tolerance to a therapeutic antibody having affinity for a cell-surface antigen, said method comprising

identifying one or more amino acid residues of the therapeutic antibody which are involved in antigen binding, and

modifying one or more of the identified amino acid residues of the therapeutic antibody to obtain the non-cell binding antibody,

wherein the non-cell binding antibody (1) has reduced affinity for antigen binding as compared to said therapeutic antibody due to said modification(s), (2) comprises at least one epitope present in the therapeutic antibody which induces an immune response, and (3) induces immunological tolerance to the therapeutic antibody.

27. The method as claimed in claim 26, wherein the amino acid residue(s) is/are identified using one or more techniques selected from the group consisting of X-ray crystallography, computer modelling, comparative modelling, CDR swapping, Alanine scanning, phage display and cycling of V-region genes.

28. The method as claimed in claim 26, wherein the amino acid residue(s) is/are modified by genetic manipulation.

29. The method as claimed in claim 28, wherein the genetic manipulation is site-directed mutagenesis.

30. The method as claimed in claim ~~26~~, wherein the affinity for antigen binding of the non-cell binding antibody is reduced to 50% or less as compared to said therapeutic antibody.

31. The method as claimed in claim 30, wherein the affinity for antigen binding of the non-cell binding antibody is reduced to 10% or less as compared to said therapeutic antibody.

E2 32. The method as claimed in claim 31, wherein the affinity for antigen binding of the non-cell binding antibody is reduced to 1% or less as compared to said therapeutic antibody.

33. The method as claimed in claim 26, wherein the non-cell binding antibody has greater than 90% amino acid sequence identity with said therapeutic antibody.

34. The method as claimed in claim 33, wherein the non-cell binding antibody has greater than 95% amino acid sequence identity with said therapeutic antibody.

35. The method as claimed in claim 34, wherein the non-cell binding antibody has greater than 99% amino acid sequence identity with said therapeutic antibody.

36. The method as claimed in claim 26, wherein the non-cell binding antibody comprises variable domains having greater than 90% amino acid sequence identity with variable domains of said therapeutic antibody.

37. The method as claimed in claim 36, wherein the non-cell binding antibody comprises variable domains having greater than 95% amino acid sequence identity with variable domains of said therapeutic antibody.

E2 38. The method as claimed in claim 37, wherein the non-cell binding antibody comprises variable domains having greater than 99% amino acid sequence identity with variable domains of said therapeutic antibody.

39. The method as claimed in claim 26, wherein the non-cell binding antibody comprises constant domains having greater than 90% amino acid sequence identity with constant domains of said therapeutic antibody.

40. The method as claimed in claim 39, wherein the non-cell binding antibody comprises constant domains having greater than 95% amino acid sequence identity with constant domains of said therapeutic antibody.

41. The method as claimed in claim 40, wherein the non-cell binding antibody comprises constant domains having greater than 99% amino acid sequence identity with constant domains of said therapeutic antibody.

42. The method as claimed in claim 41, wherein the non-cell binding antibody comprises constant domains identical with constant domains of said therapeutic antibody.

E2 43. A method of producing a fragment for inducing immunological tolerance to a therapeutic antibody having affinity for a cell-surface antigen, said method comprising fragmenting the non-cell binding antibody obtained according to the method of claim 26, said fragment (1) comprising the modification(s) of said non-cell binding antibody, (2) having reduced affinity for antigen binding as compared to said therapeutic antibody due to said modification(s), (3) comprising at least one epitope present in the therapeutic antibody which induces an immune response, and (4) inducing immunological tolerance to the therapeutic antibody.

44. The method as claimed in claim 43, wherein the fragment is a monovalent or divalent fragment of said non-cell binding antibody.

45. The method as claimed in claim 44, wherein the monovalent or divalent fragment of said non-cell binding antibody is Fab, Fab' or F(ab')<sub>2</sub>.

46. The method as claimed in claim 43, wherein the fragment is a single chain antibody.

47. The method as claimed in claim 26, further comprising expressing the non-cell binding antibody in a cell line.

48. The method as claimed in claim 47, wherein the cell line is maintained under conditions suitable for expression of said non-cell binding antibody.

E2 49. The method as claimed in claim 48, further comprising recovering said non-cell binding antibody.

50. The method as claimed in claim 49, further comprising isolating said non-cell binding antibody.

51. The method as claimed in claim 26, wherein the non-cell binding antibody comprises framework regions having greater than 90% amino acid sequence identity with framework regions of said therapeutic antibody.

52. The method as claimed in claim 51, wherein the non-cell binding antibody comprises framework regions having greater than 95% amino acid sequence identity with framework regions of said therapeutic antibody.

53. The method as claimed in claim 52, wherein the non-cell binding antibody comprises framework regions having greater than 99% amino acid sequence identity with framework regions of said therapeutic antibody.

54. The method as claimed in claim 26, wherein the modification is located in at least one of the complementarity determining regions (CDRs) of said therapeutic antibody.

E2 55. The method as claimed in claim 54, wherein the modification is located in VH CDR2.

56. The method as claimed in claim 26, wherein the modification comprises a single or a double amino acid substitution.

57. The method as claimed in claim 56, wherein the single or double amino acid substitution is located in VH CDR2.

58. The method as claimed in claim 26, wherein the therapeutic antibody has affinity for CD52.

59. The method as claimed in claim 58, wherein the therapeutic antibody is a humanised Campath-1 antibody.

60. The method as claimed in claim 26, wherein the non-cell binding antibody comprises foreign CDRs with respect to the constant region of said non-cell binding antibody.

E2 61. The method as claimed in claim 26, wherein the non-cell binding antibody comprises foreign CDRs with respect to the heavy and light chain variable domain framework regions of said non-cell binding antibody.

62. The method as claimed in claim 26, wherein the non-cell binding antibody comprises non-CDR regions of human origin.

63. The method as claimed in claim 26, wherein each of said modified amino acid residue(s) reduces the affinity for antigen binding of said non-cell binding antibody.

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64. A method of producing a non-cell binding antibody fragment for inducing immunological tolerance to a therapeutic antibody having affinity for a cell-surface antigen, said method comprising

fragmenting the therapeutic antibody to obtain said non-cell binding antibody fragment, said non-cell binding antibody fragment (1) having reduced affinity for antigen binding as compared to said therapeutic antibody due to said fragmentation, (2) comprising at least one epitope present in the therapeutic antibody which induces an immune response, and (3) inducing immunological tolerance to the therapeutic antibody.

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65. The method as claimed in claim 64, further comprising identifying one or more amino acid residues of said non-cell binding antibody fragment which are involved in antigen binding, and

modifying one or more of the identified amino acid residues of said non-cell binding antibody fragment,

wherein the non-cell binding antibody fragment has reduced affinity for antigen binding due to said modification(s).

66. The method as claimed in claim 64, wherein the non-cell binding antibody fragment is a monovalent form of said therapeutic antibody.



67. The method as claimed in claim 66, wherein the non-cell binding antibody fragment is a Fab fragment, single chain antibody, or any antibody fragment having a single binding site.

68. The method as claimed in claim 65, wherein the non-cell binding antibody fragment is a monovalent form of said therapeutic antibody.

69. The method as claimed in claim 68, wherein the non-cell binding antibody fragment is a Fab fragment, single chain antibody, or any antibody fragment having a single binding site.

E2 70. The method as claimed in claim 26, wherein the non-cell binding antibody is not a mixed molecule antibody having an H or L chain of the therapeutic antibody paired with an L or H chain of an unrelated antibody.

71. A cell line which expresses a fragment obtained according to the method as claimed in claim 43.

72. A cell line which expresses a non-cell binding antibody fragment obtained according to the method as claimed in claim 64.

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